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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,735	07/23/2007	Thomas E. Daley	11594-003-999	3147

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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,735	DALEY, THOMAS E.	
	Examiner	Art Unit	
	Yong S. Chong	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 7/7/09. Claim(s) 13-20 have been cancelled. Claim(s) 21-23 have been added. Claim(s) 1-12, 21-23 are pending. Claim(s) 1, 8, 10 have been amended. Claim(s) 1-12, 21-23 are examined herein.

Applicant's amendments have rendered all rejections of the last Office Action moot, therefore hereby withdrawn. The following new rejections will now apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for ameliorating a symptom of ethanol intolerance in a subject with reduced or absent ALDH2 activity, does not reasonably provide enablement for *preventing*. The specification does not enable any person skilled in the art to which it pertains to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set

forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the breadth of the claims; (4) the amount of direction or guidance presented; (5) the predictability or unpredictability of the art; (6) the relative skill of those in the art; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention: The rejected claims are drawn to an invention which pertains to a method of preventing and ameliorating a symptom of ethanol intolerance in a subject with reduced or absent ALDH2 activity by administering 4-MP.

(2) State of the Prior Art: The state of the art regarding ameliorating a symptom of ethanol intolerance is relatively high, however the state of the art for the prevention is non-existent.

(3) Breadth of Claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass the prevention, inhibition, and ameliorating a symptom of ethanol intolerance.

(4) Guidance of the Specification: The guidance of the specification as to the prevention of a symptom of ethanol intolerance is completely lacking. The specification discloses preventing the onset of a symptom of ethanol intolerance. However, the specification fails to mention how one is able to determine whether the onset of a symptom of ethanol intolerance in a subject would have occurred in the absence of treatment, thus being unable to confirm that prevention has indeed taken place.

Moreover, the specification fails to mention the complete prevention or cessation of a symptom of ethanol intolerance once the onset of preclinically evident stage is determined.

(5) The Predictability or Unpredictability of the Art: The invention is directed to a method of ameliorating, inhibiting, and preventing a symptom of ethanol intolerance. The specification does not disclose how one of ordinary skill in the art at the time of the invention would be able to prevent a symptom of ethanol intolerance, nor does the prior art reveal any type of prevention associated with a symptom of ethanol intolerance.

(6) The Relative Skill of those in the Art: One of ordinary skill in the art does not know how to prevent a symptom of ethanol intolerance. Moreover, one is unable to determine whether a subject will ever develop a a symptom of ethanol intolerance should this subject be administered the 4-MP.

(7) Working Examples: The specification does not give any data for the prevention of a symptom of ethanol intolerance by administering 4-MP.

(8) The Quantity of Experimentation Necessary: The specification fails to provide support for the prevention of a symptom of ethanol intolerance. Nor does it provide information to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim(s) 1-12, 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Kimizuka et al. (Japanese patent application S57-106620(5), of record) in view of Casavant et al. (Pediatrics, Vol. 107 No. 1 January 2001, of record) and Jacobsen et al. (Alcoholism: Clinical and Experimental Research, Vol. 20, pages 804-809, of record).

The instant claims are directed to a method for ameliorating a symptom of ethanol intolerance in a subject with reduced or absent aldehyde dehydrogenase subtype 2 (ALDH2) activity by administering about 0.1 to 1.0 mg/kg of 4-methylpyrazole.

Kimizuka et al. teaches on page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250

mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water ..... 15 minutes before administration of 150 ml of sake.....they were observed for symptoms for a period of two hours after the start of drinking ..... they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Furthermore, since there is a direct correlation to the above associated symptoms being exhibited after the ingestion of ethanol in individuals who have reduced or absent ALDH2; direct correlation to the loss of exhibited symptoms and treatment with 4-methylpyrazole is noted as proof of the effectiveness of 4-methylpyrazole.

Kimizuka et al. teaches on page 2 - 4 (labeled 116-118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water.

Kimizuka et al. teaches on page 2 – 4(labeled 118) of the application. There was a clinical trial stated in application 620 testing the effectiveness of 4-methylpyrazole three males who were known after the consumption of ethanol had displayed the symptoms associate with individuals who are ALDH2 deficient "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water.

Kimizuka et al. teaches on page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250

mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms."

Kimizuka et al. teaches on page 2 (pg116) the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation of alcohol to aldehyde (it is noted that it is well recognized that the form of aldehyde accumulation in alcohol metabolism is acetaldehyde) i.e. by ADH activity, page 3 (pg 117) the us of 50% inhibitory concentration (ID50) of 4-methylpyrazole against human……but as discussed above.....page 4 flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water …….. 15 minutes before administration of 150 ml of sake…….they were observed for symptoms for a period of two hours after the start of drinking …….. they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." These same individuals when they are not administered 4-MP have been repeatly noted to exhibit the symptoms addressed above.

Kimizuka et al. teaches on page 2 (pg116) the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation of alcohol to aldehyde i.e. by ADH activity, but as discussed above.....page 4 flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking….. 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride

dissolved in 50 ml water ..... 15 minutes before administration of 150 ml of sake.....they were observed for symptoms for a period of two hours after the start of drinking ..... they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Within the 620 application on page 2 (labeled 116) in the second paragraph they have directly associated the physical symptoms with the increase of aldehyde, therefore since the physical effects of aldehyde toxicity were decreased in these patients treated with 4-MP, and accumulation of aldehyde occurs due to the increased ethanol oxidizing activity of alcohol dehydrogenase in these patients, it was inherent in the method taught by the '620 application that the ethanol-oxidizing inhibiting of alcohol dehydrogenase was reduced or inhibited since the effects of aldehyde accumulation were reduced.

Kimizuka et al. teaches on page 2 (pg116) the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation of alcohol to aldehyde i.e. by ADH activity, but as discussed above.....page 4 flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water ..... 15 minutes before administration of 150 ml of sake.....they were observed for symptoms for a period of two hours after the start of drinking ..... they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms."

Kimizuka et al. teaches on page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia,

palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water ..... 15 minutes before administration of 150 ml of sake.....they were observed for symptoms for a period of two hours after the start of drinking ..... they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Additionally, this calculates out to a oral dose 4.17 - 4.55 mg/Kg of 4-MP hydrochloride, preventing or amelioration of symptom in subjects with reduced or absent aldehyde dehydrogenase subtype 2. Within the specifications they have place the about limit up to 4.4 mg/Kg.

Kimizuka et al. teaches on page 4 (label 118) of application "in three adult males, known to exhibit facial flushing and discomfort symptoms such as tachycardia, palpitations and headache upon drinking..... 55 to 60 kg..... orally administered 250 mg of 4-methylpyrazole hydrochloride dissolved in 50 ml water ..... 15 minutes before administration of 150 ml of sake.....they were observed for symptoms for a period of two hours after the start of drinking ..... they hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms." Additionally, the range stated in the "620 publication" calculates out to a oral dose 4.17 - 4.55 mg/Kg of 4-MP hydrochloride, preventing or amelioration of symptom in subjects with reduced or absent aldehyde dehydrogenase subtype 2. Within the specifications they have place the about limit up to 4.4 mg/Kg.

Casavant et al. teaches that the free base form of 4-MP, which has the trade name Fomepizole (Antizol), is well known in the art. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the free

base form of 4-MP for the salt form because of the functional equivalency of the two forms. It is further obvious to administer 4-MP before or during consumption of alchohol since it is known, in general, to treat symptoms of ethanol intolerance. Oral or transdermal administration of active agents are well known in the art.

Kimizuka et al. teaches as discussed above, however fail to specifically disclose administration of 4-MP in the claimed amount of about 0.1 to 1.0 mg per kg of body mass.

Jacobsen et al., teaches that lower doses of 4-MP was effective in treatment but yet did not have the undesirable side effects of larger doses of 4-MP, such as decreased ethanol elimination rate.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have administered 4-MP in the amount 0.1 to 1.0 mg per kg of body mass to a subject with ethanol intolerance.

A person of ordinary skill in the art would have been motivated to administer 4-MP in the amount 0.1 to 1.0 mg per kg of body mass to a subject with ethanol intolerance because Jacobsen et al., in general, teaches that lower doses of 4-MP was effective in treatment but yet did not have the undesirable side effects of larger doses of 4-MP, such as decreased ethanol elimination rate. It is well known that there are varying degrees of symptoms; therefore the skilled artisan knows to optimize the dosage or amounts of active agents based on the severity of the disorder, age, sex, condition, weight, etc. Therefore, one of ordinary skill in the art would have had a

reasonable expectation of success in treating ethanol intolerance by administering 4-MP in the amount 0.1 to 1.0 mg per kg of body mass.

Generally, mere optimization of ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382; It has been held that it is within the skills in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. *In re Boesch*, 205 USPQ 215 (CCPA 1980) MPEP 2114.04

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S. Chong/
Primary Examiner, Art Unit 1627

YSC